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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Kirk Hogan		
Serial No.:	09/613,887	Group No.:	1634
Filed:	July 11, 2000	Examiner:	J.A. Goldberg
Entitled:	**Methods and Compositions for Perioperative Genomic Profiling**		

TRANSMITTAL OF CORRECTED APPEAL BRIEF (PATENT APPLICATION - 37 CFR § 192)

Mail Stop Appeal Brief - Patents
Commissioner for Patents
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Dated: September 19, 2005 **By:** Mary Ellen Waite
Mary Ellen Waite

Sir or Madam:

1. Transmitted herewith, in triplicate, is the CORRECTED APPEAL BRIEF in this application, with respect to the Notice of Appeal filed concurrently with this application.

2. STATUS OF APPLICANT

   This application is behalf of other than a small entity.

3. FEE FOR FILING APPEAL BRIEF

   Filing Fee submitted with the original filing of the Appeal Brief dated 6/07/05

4. EXTENSION OF TERM

   No extension fees are due at this time.

5. TOTAL FEE DUE

   No fee is due at this time.

6. FEE DEFICIENCY

   If any additional fee is required, charge Account No. 08-1290.

Dated: September 19, 2005

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PATENT
Attorney Docket No. **HOGAN-04448**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Kirk Hogan		
Serial No.:	09/613,887	Group No.:	1634
Filed:	July 11, 2000	Examiner:	J.A. Goldberg
Entitled:	**Methods and Compositions for Perioperative Genomic Profiling**		

CORRECTED APPELLANT'S BRIEF

APPEAL NO.:

CERTIFICATE OF FACSIMILE TRANSMISSION UNDER 37 C.F.R. § 1.8(a)(1)(i)(B)

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being deposited with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Appeal Brief – Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

9-19-05

By: Mary Ellen Waite

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Madam/Sir:

This Corrected Appellant's Brief is in furtherance of the Notice of Appeal filed June 7, 2005, and in response to the Notice of Non-Compliant Appeal Brief mailed August 18, 2005. The Brief has been corrected in accord with 37 CFR §41.37 to include: "A concise explanation of the subject matter defined in each of the independent claims involved in the appeal which shall refer to the specification by page and line number, and to the drawing, if any, by reference character."

The fees required under SS 1.17(h) and any required Petition for Extension of time for filing this Brief and fees therefore are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF.

This Brief is transmitted in triplicate. [37 CFR SS 1.192(a).]

This Brief contains these items under the following headings and in the order set forth below [37 CFR SS 1.192(c)]:

I. REAL PARTY IN INTEREST

The real party in interest is the inventor of record, Kirk Hogan.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to the Appellant or to the Appellant's legal representative.

III. STATUS OF CLAIMS

Claims 1-20 were filed in the original application. During prosecution of the application, Claims 1-20 were cancelled and Claims 21-41 were added in the Amendment and Response to Final Office Action filed August 9, 2001. Claims 21-41 were cancelled and Claims 42-73 were added in the Amendment and Response to Final Office Action filed January 14, 2003. Claims 42-73 were cancelled and Claims 74-105 were added in the Amendment and Response to Office Action filed January 5, 2004. Claims 74-105 have been rejected by the Office in the Final Office Action dated January 11, 2005. No other Claims are pending. Therefore, Claims 74 -105 are pending in this appeal. Appellant appeals the Final Office Action of January 11, 2005.

The Claims, as they now stand, are set forth in the Claims Appendix.

IV. STATUS OF THE AMENDMENTS

All previous amendments have been entered.

V. SUMMARY OF THE CLAIMED SUBJECT MATTER

The present invention relates to methods for perioperative genomic screening of surgical subjects, in particular to perioperative screening for nucleic acid genetic markers indicative of responses to anesthesia, and to other perioperative or operative treatments and procedures. In current clinical practice, there is no technology available that provides the information of the perioperative genomic profiles of the present invention. In the past, screening tests of a patient's phenotype (*e.g.*, blood cell count and chemistries, urinalysis, electrocardiogram (EKG), and chest X-ray) were routinely performed prior to surgery. However, the present-day procedure for screening for

susceptibility to heritable disorders of consequence in the interval surrounding surgery does not look at nucleic acid genetic markers, and is limited to asking a patient if they or their family members have had any previous difficulties with anesthesia or surgery. The use of laboratory phenotypic tests for patients prior to surgery has generally been reduced or eliminated. Reasons for elimination include the inaccuracy and lack of specificity of the various phenotypic tests, the aggregate costs of many different kinds of phenotypic screening tests necessary to assemble test panels, and uncertainty as to how to alter treatment course of action in response to phenotypic test results. Accordingly, contemporary anesthesiology and surgery textbooks emphasize that recent studies indicate a lack of benefit from phenotypic testing as a method of assessing patients before surgery, and stress that cost-benefit strategies can only be justified when laboratory testing is reduced to that indicated by history-taking.

The perioperative genomic profiles of the present invention stand in direct contrast to the panels of phenotypic tests currently available and previously used. In the present invention, genetic alleles are tested in ensemble according to selection categories and criteria taught by the present invention, in order to construct a personalized perioperative genomic profile. The perioperative genomic profiles of the present invention may be used, for example, to select the safest and most effective anesthetic regimen and surgical procedure, and to begin life-saving interventions as soon as possible. The perioperative genomic profiles of the present invention thereby solve many of the problems described above that have led practitioners away from preoperative phenotypic testing. The perioperative genomic profiles of the present invention are cost and time effective. As taught by the present invention, genomic markers are selected for inclusion in the profile by virtue of their analytical validity (*i.e.*, a high level of accuracy, specificity, and predictive value), clinical validity (*i.e.*, a high level of correlation between DNA sequence variation and the trait of interest) and clinical utility (*i.e.*, a significant impact of the test result on the patient's well-being during and after surgery). The perioperative genomic profiles of the present invention thus allow for the individualization of treatment options for each subject undergoing a surgical procedure. In this fashion, the present invention provides a novel diagnostic tool currently unavailable in the surgical field, enabling solutions for problems that have no available

alternatives. In the absence of any competing technology for quantifying subject's genetic contributors to perioperative risk, the present invention provides life- and cost-saving information to caregivers on an accelerated and amplified scale relative to current diagnostics.

In one embodiment of the present invention, a method is described wherein a patient is screened perioperatively to determine a risk for complications during a surgical procedure (described, for example, in the Specification at page 1, line 10 – page 3, line 4, and page 21 lines 28 – page 22, line 8) associated with known genetic variations (described, for example, at Figure 1, "Alleles, Markers, Mutations", Figure 2, "Genomic data", page 25, lines 19-25, and page 26, line 9 – page 27, line 14), comprising obtaining a sample (described, for example, at page 24, line 23 - page 25, line 2) from a perioperative subject (described, for example, at page 3, line 15, page 25, lines 3-4, Figure 2, "Sample", page 21, lines 23-27, and Example page 46, lines 22-25), wherein the perioperative subject is a patient scheduled for a surgical procedure that has not yet completed the surgical procedure, subjecting the sample to an assay (described, for example, at page 24, line 20 –22, Figure 1, "Detection Technique", page 24, lines 5-10, "Examples of Detection Techniques" page 25, line 26 - page 26 line 5, "Assays for Generating Genomic Profiles" page 34, line 15 – page 42, line 2, and "Experimental" example page 46, line 26 – page 47, line 25) for detecting two or more nucleic acid genetic markers (described, for example, at page 3, line 16, and page 4, line 5), in two or more genes associated with two or more conditions to generate a genomic profile (described, for example, at page 3, line 17, Figure 1, "Genomic Profile", page 23, lines 6-10, and page 24, lines 21-22) for use in selecting a perioperative course of action (Figure 1, "Alter Intervention"), wherein the subjecting step occurs after the patient is scheduled for surgery, but before completion of the surgical procedure, thereby determining a risk for complications (described, for example, at page 1, line 10 – page 3, line 4, and page 21, line 28 – page 22, line 8) during the surgical procedure. In some embodiments the course of action comprises administration of anesthesia during a surgical procedure (described, for example, at page 4, lines 23-25, and page 33, line 15 - page 34, line 14). In other embodiments the surgical procedure is non-invasive surgery (described, for example, at page 3, lines 22-23, and page 22 lines 12-13). In another embodiment the surgical procedure is invasive surgery (described, for example, at page 3, line 22, and page 22, lines 13- 17). In yet another embodiment the course

of action comprises administration of anesthesia during a medical procedure (described, for example, at page 4, lines 4- 10). In a further embodiment the genomic profile comprises information pertaining to a pharmacodynamic risk (described, for example, at page 3, lines 24-25, page 4, lines 25-26, page 23, lines 13-17, and page 29, lines 6-10). In still further embodiments the genomic profile comprises information pertaining to a pharmacokinetic risk (described, for example, at page 3, lines 25-26, page 4, lines 26-27, page 23, lines 13-17, and page 26, lines 10 – 14). In another embodiment the genomic profile of the present invention comprises presymptomatic diagnosis (described, for example, at page 3, lines 26-27, and page 4, lines 27-28). In additional embodiments the genomic profile comprises information pertaining to differential diagnosis of co-existing diseases (described, for example, at page 3, lines 26-28, page 4, lines 28-29, page 7, lines 2-4, page 23, lines 25-19, page 29, lines 15-20, page 31, line 25 – page 33, line 3, and page 33, lines 4-14). In some embodiments the two or more nucleic acid genetic markers comprise mutations in two or more genes, wherein the genes are selected from the group consisting of *BChE*, *CYP2D6*, *MTHFR*, *MTR*, *CBS*, *F2*, *F5*, *RYR1*, *CACNA1S*, and *CPT2* (described, for example, at page 4, lines 1-3, and page 4, lines 18-19). In some embodiments the two or more nucleic acid genetic markers comprise 5 or more mutations in two or more genes (described, for example, at page 28, lines 8-9). In still further embodiments the two or more nucleic acid genetic markers comprise 10 or more mutations in two or more genes (described, for example, at page 28, lines 9-10). In one embodiment of the present invention the method further comprises using the genomic profile of the present invention for selection of conditions for a surgical procedure carried out on the patient (described, for example, at page 46, "Perioperative Screening for Anesthesia Markers, line 14).

In one embodiment of the present invention a method is described for selecting conditions for a surgical procedure by screening a patient perioperatively to determine a risk for complications (described, for example, in the Specification at page 1, line 10 – page 3, line 4, and page 21, line 28 – page 22 line 8) during a surgical procedure associated with known genetic variations (described, for example, at Figure 1, "Alleles, Markers, Mutations", Figure 2, "Genomic Data", page 25, lines 19-25, and page 26, line 9 – page 27 line 14) comprising providing a sample (described, for example, at page 24, line 23 - page 25, line 2) from a perioperative subject, wherein the perioperative subject (described, for example, at page 3,

line 15, page 25, lines 3-4, Figure 2, "Sample", page 21, lines 23-27, and Example, page 46 lines 22-25), is a patient scheduled for a surgical procedure and has not yet completed the surgical procedure, and subjecting the sample to an assay (described, for example, at page 24, lines 20 –22, Figure 1, "Detection Technique", page 24, lines 5-10, "Examples of Detection Techniques" page 25, line 26 - page 26, line 5, "Assays for Generating Genomic Profiles" page 34, line 15 – page 42, line 2, and "Experimental" example page 46, line 26 – page 47, line 25) for detecting two or more nucleic acid genetic markers (described, for example, at page 3, line 16, and page 4, line 5) in two or more genes known to be associated with two or more perioperative phenotypes to generate a genomic profile (described, for example, at page 3, line 17, Figure 1, "Genomic Profile", page 23, lines 6-10, and page 24, lines 21-22) for use in selecting a perioperative course of action (described, for example, at Figure 1 "Alter Intervention"), for use in selecting a surgical procedure treatment course of action (described, for example, at page 7, lines 6-7, page 23, lines 2-4, and page 26, lines 24-26), and subjecting the subject to a surgical procedure. In some embodiments of the present invention the genetic markers are associated with a pharmacological response (described, for example, at page 4, lines 11-13). In other embodiments the pharmacological response is to an anesthetic (described, for example, at page 4, lines 15-16). In other embodiments the pharmacological response is to drugs used in anesthetic practice (described, for example, at page 4, lines 11-16). In a further embodiment of the present invention the two or more nucleic acid genetic markers comprise a mutation in two or more genes associated with two or more conditions, wherein the genes are selected from the group consisting of *BChE, CYP2D6, MTHFR, MS, CBS, F2, F5, RYR1, CACNA1S, and CPT 2* (described, for example, at page 4, lines 1-3, and page 4, lines 18-19). In some embodiments the two or more nucleic acid genetic markers comprise 5 or more mutations in two or more genes (described, for example, at page 28, lines 8-9). In still further embodiments the two or more nucleic acid genetic markers comprise 10 or more mutations in two or more genes (described, for example, at page 28, lines 9-10).

In one embodiment of the present invention a method is described of screening a patient perioperatively to determine a risk for complications during a surgical procedure (described, for example, in the Specification at page 1, line 10 – page 3, line 4, and page 21 lines 28 – page 22 line 8) from known genetic variations (described, for example, at Figure 1, "Alleles, Markers, Mutations", Figure 2, "Genomic Data", page 25, lines 19-25, and page 26,

line 9 – page 27, line 14) comprising obtaining a sample (described, for example, at page 24, line 23 - page 25, line 2) from a perioperative subject (described, for example, at page 3, line 15, page 25, lines 3-4, Figure 2, "Sample", page 21, lines 23-27, and "Experimental" example xample page 46, lines 22-25), wherein the perioperative subject is a patient scheduled for a surgical procedure that has not yet completed the surgical procedure, and subjecting the sample to an assay (described, for example, at page 24, lines 20 –22, Figure 1, "Detection Technique", page 24, lines 5-10, "Examples of Detection Techniques" page 25, line 26 - page 26, line 5), "Assays for Generating Genomic Profiles" page 34, line 15 – page 42, line 2, and "Experimental" example page 46, line 26 – page 47, line 25) for detecting two or more nucleic acid genetic markers in two or more genes clinically associated with two or more conditions selected from the group consisting of butyrylcholinesterase deficiency (described, for example, at page 2, lines 9-16, page 30, line 24 - page 31, line 2, and Table 1, page 48), impaired debrisoquine metabolism (described, for example, at page 2, lines 17-21, page 31, lines 3-9, and Table 2, page 48), thrombosis (described, for example, at page 6, line 24, page 32, lines 5 – 18, and Table 3, page 48), and malignant hyperthermia (described, for example, at page 1, line 25 -page 2, line 4, page 31, lines 14-24, and Table 4, page 49) to generate a genomic profile (described, for example, at page 3, line 17, Figure 1, "Genomic Profile", page 23, line 6-10, and page 24, line 21-22), wherein said genomic profile provides information for use by a physician in determining a risk for complications during a surgical procedure (described for example at Figure 1, "Alter Intervention" and Figure 2, "Genomic Profile – Interpretation and Dissemination – Clinical Data"). In one embodiment the course of action comprises administration of anesthesia during a surgical procedure (described, for example, at page 4, lines 23-25, and page 33, line 15 - page 34, line 14). In another embodiment the surgical procedure is non-invasive surgery (described, for example, at page 3, line 22, and page 22, lines 13- 17). In a further embodiment the surgical procedure is invasive surgery (described, for example, at page 3, lines 22-23, and page 22, lines 12-13). In a still further embodiment the method further comprises the step of using the genomic profile for selection of conditions for a surgical procedure carried out on the patient (described, for example, at page 7, lines 6-7, page 23, lines 2-4, and page 26, lines 24-26). In some embodiments the two or more nucleic acid genetic markers comprise 5 or more mutations in two or more genes (described, for example, at page 28, lines 8-9). In still further embodiments the two or more

nucleic acid genetic markers comprise 10 or more mutations in two or more genes (described, for example,
at page 28, lines 9-10).

In one embodiment of the present invention, a method is described of screening a patient perioperatively to determine a risk for complications during a surgical procedure (described in the Specification, for example, at page 1, line 10 – page 3, line 4, and page 21, lines 28 – page 22, line 8) from known genetic variations (described, for example, at Figure 1, "Alleles, Markers, Mutations", Figure 2, "Genomic Data", page 25, lines 19-25, and page 26, line 9 – page 27 line 14), comprising obtaining a sample (described, for example, at page 24, line 23 - page 25, line 2) from a perioperative subject (described, for example, at page 3, line 15, page 25, lines 3-4, Figure 2, "Sample", page 21, lines 23-27, and "Experimental" example page 46, lines 22-25), wherein the perioperative subject is a patient scheduled for a surgical procedure that has not yet completed the surgical procedure, and subjecting the sample to an assay (described, for example, at page 24, lines 20 –22, Figure 1, "Detection Technique", page 24, lines 5-10, "Examples of Detection Techniques" page 25, line 26 - page 26, line 5), "Assays for Generating Genomic Profiles" page 34, line 15 – page 42, line 2, and "Experimental" example page 46, line 26 – page 47, line 25), for detecting two or more nucleic acid genetic markers in two or more genes clinically associated with butyrylcholinesterase deficiency (described, for example, at page 2, lines 9-16, page 30, line 24 - page 31, line 2, and Table 1, page 48), and impaired debrisoquine metabolism (described, for example, at page 2, lines 17-21, page 31, lines 3-9, and Table 2, page 48), to generate a genomic profile (described, for example, at page 3, line 17, Figure 1 "Genomic Profile", page 23, lines 6-10, page 24, lines 21-22), wherein the genomic profile provides information for use by a physician in determining a risk for complications during a surgical procedure (described for example at Figure 1, "Alter Intervention", and Figure 2, "Genomic Profile – Interpretation and Dissemination – Clinical Data").

In one embodiment of the present invention a method is described for selecting an appropriate anesthesia treatment during surgery (described in the Specification, for example, at page 2 line 23 - page 3, line 4, page 3, line18, and page 22, line 18 – page 23, line 5), comprising providing a sample (described, for example at page 24, line 23 - page 25, line 2) from a perioperative subject (described, for example, at page 3, line15, page 25, lines 3-4,

Figure 2, "Sample", page 21, lines 23-27, and "Experimental" example page 46, lines 22-25), wherein the perioperative subject is a patient scheduled for a surgical procedure that has not yet completed the surgical procedure, and subjecting the sample to an assay (described, for example, at page 24, lines 20 –22, Figure 1, "Detection Technique", page 24, lines 5-10, "Examples of Detection Techniques" page 25, line 26 - page 26, line 5), "Assays for Generating Genomic Profiles" page 34, line 15 – page 42, line 2, and "Experimental" example page 46, line 26 – page 47, line 25), that detects a first marker in a first gene and a second marker in a second gene to generate assay results, wherein the markers are known to be associated with adverse responses to anesthesia treatment (described, for example, at page 6, lines 19-24, and page 30, lines 15-20), and subjecting the subject to a surgical procedure, wherein the assay results are consulted in selecting an appropriate anesthesia treatment for the subject (described, for example, at Figure 1, "Alter Intervention"). In one embodiment the selecting step comprises selection of dosages of anesthesia (described, for example, at page 1, line 17, and page 2, lines 20-21). In another embodiment the selecting step comprises selection of anesthesia compounds (described, for example, at page 1, line 17, page 28, lines 17-19, and page 47, line 27). In a further embodiment the selecting step comprises selection of monitoring procedures (described, for example, at page 7, lines 7-12, and page 47, line 27).

VI. GROUND OF REJECTION TO BE REVIEWED ON APPEAL

There is one ground of rejection involved in the present appeal:

Ground of rejection – Whether Claims 74-94 and 96-105 are obvious over Miller (Anesthesia, Vol. 2, pages 1323-1333, 1981) (hereinafter "Miller") in view of Quane *et al.* (Human Molecular Genetics, Vol 3, No. 3, page 471-476, 1994) (hereinafter "Quane") or Acta Anaesthesiologica Scandinavica (Vol 39, page 139-141, 1995) (hereinafter "Acta") and La Du (Cellular and Molecular Neurobiology, Vol 11, No. 1, page 79-89, 1991) (hereinafter "La Du") or Pharmacogenetics (Chapter 4, pages 309-326, IDS #201) (hereinafter "Pharmacogenetics") and Evans *et al.* (Science, Vol 286, pages 487-491, October 1999) (hereinafter "Evans') or Poort *et al.* (Blood, Vol 88, No 10, page 3698-3703, 1996) (hereinafter "Poort'), and further in view of Hoon *et al.* (US Pat. 6,057,105, May 2, 2000) (hereinafter "Hoon") and Hacia (Nature Genetics Supplement, Vol. 21, pages 42-47, January, 1999) (hereinafter "Hacia").

VII. ARGUMENT

A. Ground of Rejection – Claims 74-94 and 96-105 are Not Obvious Over the Combination of Miller in view of Quane, or in view of Acta and La Du, or in view of Pharmacogenetics and Evans, or in view of Poort, and further in view of Hoon and Hacia.

Section 103 of title 35 of the United States Code states:

> A patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. (35 U.S.C. § 103 (a) (2000).

In assessing the differences between the subject matter sought to be patented and the prior art, §103 requires the Examiner to appraise the claimed invention "as a whole". Typically inventions are new combinations of existing principles or features.[1] The "as a whole" instruction to the Examiner in title 35 prevents evaluation of the invention piece-by-piece. Without this statutory requirement, the Examiner's obviousness assessment risks breaking an invention into its component parts (A + B + C), then find a prior art reference containing A, another containing B, and another containing C, and on that basis, and no other, declaring the invention obvious. In the Final Office Action of January 11, 2005 the Examiner has fallen into this trap, or more accurately in the present case, the Examiner has fallen into the trap of finding A + (B or C) + (D or E) + (F or G) + H + I (*i.e.*, "Miller" plus "Quane" or "Acta" plus "La Du" or "Pharmacogenetics" plus "Evans" or "Poort" plus "Hoon" plus "Hacia".)

A *prima facie* case of obviousness requires the Examiner to cite a reference, or a combination of references, that (a) discloses all of the elements of the claimed invention,

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1 Envtl. Designs, Ltd. V. Union Oil Co., 713 F.2d 693, 698 (Fed. Cir. 1983) (noting that "virtually all [inventions] are combinations of old elements").

(b) provides a suggestion or motivation to one of skill in the art to combine the elements to yield the claimed combination, and (c) provides a reasonable expectation of successfully carrying out the claimed combination. Failure to establish any one of the three requirements precludes a finding of a *prima facie* case of obviousness, and, without more, entitles the Appellant to allowance of the claims at issue.[2] The Appellant contends that Examiner has failed to establish a *prima facie* case of obviousness because:

1) **The Examiner's combination of references does not teach all elements of the claims;**
2) **The Examiner has not provided a suggestion or motivation to combine the references; and**
3) **The evidence of record directly refutes the Examiner's rejection, and has not been properly considered**

1. The Examiner's Combination of References Does Not Teach All Elements of The Claims

During the prosecution of the present application, the Appellant has drawn the Examiner's attention on multiple occasions to the fact that, even taken in aggregate, the Examiner's combinations of Miller, Quane, Acta, LaDu, Pharmacogenetics, Evans, Poort, Hoon and Hacia fail to teach all elements of the claims. (See, for example, Amendment and Response to Office Action mailed March 23, 2004, page 17.) Specifically, the Examiner's combinations fail to teach, suggest or even mention:

Claim 74 - "a genomic profile for use in selecting a perioperative course of action"

Claim 87 – "a genomic profile for use in selecting a surgical treatment course of action"

Claims 94 and 101 – "a genomic profile, wherein said genomic profile provides

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2 *See, e.g.,* Northern Telecom Inc. v. Datapoint Corp., 15 USPQ2d 1321, 1323 (Fed. Cir. 1990).

information for use by a physician in determining a risk for complications during a surgical procedure"

Claim 102 – "an assay that detects a first marker in a first gene and a second marker in a second gene to generate assay results, wherein said assay results are consulted in selecting an appropriate anesthesia treatment"

Confronted by the Appellant's exhibit of these missing elements, the Examiner has remained silent. For example, in the Final Office Action mailed January 11, 2005 the Examiner fails to respond to the Appellant's express showing of this deficiency. This is because nowhere in the Examiner's combinations of references are these elements to be found.

Nor are these the only elements missing from the Examiner's combinations. None of the Examiner's cited references alone or in combination teach, suggest or even mention:

Claims 76 - "The method of Claim 75, wherein said surgical procedure is non-invasive surgery."

Claim 78 – "The method of Claim 74, wherein said course of action comprises administration of anesthesia during a medical procedure."

Claim 81 – "The method of Claim 74, wherein said genomic profile comprises a presymptomatic diagnosis."

Claim 83 - "The method of Claim 74, wherein said two or more nucleic acid genetic markers comprise mutations in two or more genes associated with two or more conditions, said genes selected from the group consisting of *BChE, CYP2D6, MTHFR, MS, CBS, F2, F5, RYR1, CACNA1S, and CPT.*"

Claim 84 - "The method of Claim 83, wherein said two or more nucleic acid genetic markers comprise 5 or more mutations in two or more genes associated with two or more conditions to generate a genomic profile for use in selecting a perioperative course of action."

Claim 85 – "The method of Claim 83, wherein said two or more nucleic acid genetic markers comprise 10 or more mutations in two or more genes

associated with two or more conditions to generate a genomic profile for use in selecting a perioperative course of action."

Claim 86 - "The method of Claim 74, further comprising the step of: c) using said genomic profile for selection of conditions for a surgical procedure carried out on said patient."

Claim 91 - "The method of Claim 87, wherein said two or more nucleic acid genetic markers comprise mutations in two or more genes associated with two or more conditions, said genes selected from the group consisting of *BChE, CYP2D6, MTHFR, MS, CBS, F2, F5, RYR1, CACNA1S, and CPT.*"

Claim 92 - "The method of Claim 91, wherein said two or more nucleic acid genetic markers comprise 5 or more mutations in two or more genes known to be associated with two or more perioperative phenotypes."

Claim 93 - "The method of Claim 91, wherein said two or more nucleic acid genetic markers comprise 10 or more mutations in two or more genes known to be associated with two or more perioperative phenotypes."

Claim 96 - "The method of Claim 94, wherein said surgical procedure is non-invasive surgery."

Claim 98 – "The method of Claim 94, further comprising the step of: c) using said genomic profile for selection of conditions for a surgical procedure carried out on said patient."

Claim 103 – "The method of Claim 102, wherein said selecting of an appropriate anesthesia treatment comprises selection of dosages of anesthesia"

Claim 105 – "The method of claim 102, wherein said selecting of an appropriate anesthesia treatment comprises selection of monitoring procedures."

The Examiner has never divulged to the Appellant where these missing elements are to be located in the Examiner's cited prior art.

The Court of Appeals for the Federal Circuit sets forth the Examiner's obligation as follows:

"In determining obviousness, the invention must be considered as a whole without the benefit of hindsight, and the claims must be considered in their entirety."[3]

To the contrary, the Appellant contends that the Examiner has manifestly not considered the claims of the present invention in their entirety, and has not considered the invention as a whole. Despite having engaged in far-reaching hindsight analysis (discussed below), the Examiner has nevertheless failed to identify all of the elements of the presently claimed invention in the prior art. As a consequence, the Examiner's cited references do not remedy one another's defects in combination. In view of the above, the Appellant respectfully requests that the rejection be withdrawn.

2. The Examiner Does Not Provide a Proper Suggestion or Motivation to Combine References

The Court of Appeals for the Federal Circuit has provided further assurance of an "as a whole" assessment of the invention under 35 U.S.C. §103 by requiring a showing by the Examiner that the prior art provides "a reason, suggestion, or motivation to lead an inventor to combine those references."[4] As well, the court holds that "The range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular. Broad conclusory statements regarding the teaching of multiple references, standing alone, are not "evidence"."[5] (Emphasis added.)

In attempting to meet these requirements, in the Final Office Action of January 11, 2005, the Examiner argues:

"The Examiner has set for a prima facie case which combines all of the teachings and motivations specifically enumerated in the art to obtain the claimed invention as a whole (see rejection above)." (Final Office Action of January 11, 2005, page 12.) (Emphasis added.)

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3 *Rockwell International Corp. v. United States*, 147 F.3d 1358, 47 USPQ2d 1027 (Fed. Cir. 1998).

4 *Pro-Mold and Tool Co. v. Great Lakes Plastics Inc.*, 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996).

5 *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999).

And:

> "Therefore the Examiner has provided a combination of references reflecting the state of the art at the time the invention was made which renders the claims obvious and provides explicit motivation for performing such methods as required by the instant claims. (Final Office Action of January 11, 2005, page 17.) (Emphasis added).

In the Final Office Action of January 11, 2005 the Examiner finds "explicit motivation" to make the Examiner's combinations in one prior art reference, *i.e.*, Quane. The Appellant contends that Quane falls short of providing a teaching, suggestion or motivation to combine the Examiner's references in meeting the Patent and Trademark Office's obligation under 35 U.S.C. §103. To the contrary, there is nothing in the prior art singly, or as a whole, to suggest the desirability and thus the obviousness of making the combination in a way that would produce the claimed invention.

a.) Quane Does Not Provide a Proper Suggestion or Motivation to Combine References

The only reference the Examiner provides as evidence for a motivation to combine the Examiner's selection of references is Quane, entitled "Detection of a novel common mutation in the ryanodine receptor gene in malignant hyperthermia: implications for diagnosis and heterogeneity studies". The Examiner argues:

> "The examiner's position is not based upon improper hindsight. The art clearly provides the motivation. Quane, for example teaches that once an individual is diagnosed as being susceptible to MH, the anaesthetics which trigger this syndrome can be avoided." This explicit teaching to avoid anaesthetics which trigger MH is motivation to avoid administering anesthetics to patients with particular mutations. Therefore, the combination of references is permissible." (Final Office Action of January 11, 2005, page 24.) (Emphasis added.)

The Examiner is mistaken. The Examiner's combination is not permissible because Quane does not provide motivation to combine the Examiner's cited references. Quane is directed to a single gene, *i.e.*, the ryanodine receptor gene, and a single condition, *i.e.*, malignant hyperthermia, and testing patients after the adverse clinical event. Clearly, Quane does not teach, motivate or suggest a combination of references for obtaining a sample from a perioperative subject scheduled for a surgical procedure that has not yet been completed, and subjecting the sample to an assay for detection of two or more nucleic acid genetic markers in two or more genes associated with two or more conditions to generate a genomic profile for use in selecting a perioperative course of action. Specifically, Quane makes no mention, teaching or suggestion of any other gene or condition taught by the Appellant's Claims and Specification, or by the Examiner's cited references. Quane does not mention, suggest, teach or motivate any combination of references as the Examiner alleges in error. Moreover, Quane provides no reason to combine any of the elements of the Examiner's other references, nor do any of the Examiner's other references motivate, teach or suggest this combination. In point of fact, Quane has no teaching whatsoever to make the Examiner's combination.

Indeed, as a matter of record, the Examiner concedes that Quane does not teach, suggest or motivate the detection of two or more nucleic acid genetic markers in two or more genes associated with two or more conditions to generate a genomic profile in a sample from a perioperative subject for use in selecting a perioperative course of action of the present invention. For example, the Examiner argues:

> "The claims are drawn to detecting two or more genetic markers to generate a genomic profile useful in selecting (a) perioperative course of action. The claims are not drawn to diagnosing MH. The claims are drawn to screening a patient perioperatively to determine a risk for complications; a method for selecting conditions for a surgical procedure; a method of screening a patient perioperatively to determine a risk for complications during said surgical procedure." (Office Action 03/23/2004, page 18.) (Emphasis added.)

Thus, the Examiner is expressly aware of the gap between the Examiner's combination of references and the present invention, that is, the absence of a motivation or suggestion in Quane to combine the Examiner's cited references to arrive at the present invention.

In reply to the Appellant's response that Quane is directed to only a single gene (*i.e.*, the ryanodine receptor gene) associated with a single condition (*i.e.*, malignant hyperthermia), in the Final Office Action of January 11, 2005 the Examiner argues:

> "This argument has been thoroughly reviewed, but is not found persuasive because Quane provides the motivation to avoid triggering of a condition which has been associated with a mutation." (Final Office Action of January 11, 2005, page 14.) (Emphasis added.)

Hence, the Examiner's inflated interpretation of Quane allegedly renders obvious any claim drawn to avoidance "of a condition which has been associated with a mutation". In referring to Quane, the Examiner continues:

> "Thus the concept of determining a genotype to prevent and/or avoid syndromes was gleaned from the prior art." (Final Office Action of January 11, 2005, page 17). (Emphasis added.)

And:

> "While the particular teachings of Quane are directed to MH, using genetic information to prevent or avoid certain conditions is broadly taught by Quane." (Final Office Action of January 11, 2005, page 15.) (Emphasis added.)

According to the Examiner's analysis, any claims directed to the use of genetic information for the prevention or avoidance of any condition or any syndrome, are rendered obvious by Quane after 1994. Tellingly, the Examiner does not point to particular language in Quane making this broad teaching. To the contrary, the Appellant contends that Quane teaches no such thing (*i.e.*, that Quane teaches but one gene and one

condition), and that the Patent and Trademark Office recognizes no such standard (*i.e.*, that Quane renders obvious all claims drawn to determining a genotype to prevent and/or avoid syndromes after 1994). Under the proper evidentiary standard, Quane standing alone, or in combination with others of the Examiner's references, fails to provide motivation to combine the references and thereby arrive at the perioperative genomic profiles of, for example, Claims 74, 87, 94, 101 or 102. In contrast, the Appellant has provided specific and direct evidence contrary to the Examiner's misreading of Quane (First Declaration of Dr. Kirk Hogan, February 8, 2002, Second Declaration of Dr. Kirk Hogan, July 8, 2002).

b.) The Examiner's "Preventing Death and/or Pain and Suffering" Is Not The Law Under 35 U.S.C. §103

In the Final Office Action of January 11, 2005, the Examiner errs further in setting forth, for the first time, an even more all-encompassing standard for the identification of a teaching, suggestion or motivation to combine references. Still relying on the Quane reference (*i.e.*, teaching one gene and one condition), the Examiner argues:

> "Quane teaches that once the individual is diagnosed as being susceptible to MH, the anesthetics which trigger the syndrome can be avoid(ed). Quane thus contemplates and suggests avoiding death and pain and suffering." (Final Office Action of January 11, 2005, page 15.) (Emphasis added.)
>
> And:
>
> "While the response asserts that there is no motivation or evidence, it is unclear whether the applicant is suggesting that the motivation to prevent death and/or pain and suffering is not a motivation." (Final Office Action of January 11, 2005, page 15.) (Emphasis added.)
>
> And:

"Thus in 1994, prior to the instant invention, the artisan was attentive to the need to prevent and avoid events which may trigger death and/or pain and suffering. The examiner is unclear why the response would not find that preventing death and/or pain and suffering would be a motivation recognized by one of ordinary skill in the art at the time the invention was made." (Final Office Action of January 11, 2005, pages 15 – 16.) (Emphasis added.)

Hence, under the Examiner's runaway interpretation of Quane, an invention made after 1994 that prevents death and/or pain and suffering is rendered obvious by virtue of Quane's motivation to combine such references that the Examiner might chose. The Appellant contends that the Examiner's novel "prevention of death and/or pain and suffering" standard is not the law as expressed in statute, case law or the MPEP. If, in keeping with the Examiner's deduction, a motivation or suggestion to combine references is to be found in the ordinary artisan's desire to avoid death and/or pain and suffering, a preponderance of life science inventions are henceforth unpatentable. The Appellant contends that motivation to test for a single condition or syndrome associated with a single gene, as in Quane, is not factual evidence of motivation to combine the Examiner's references in reconstructing the present invention. Contrary to the Examiner's arguments, the motivation to combine the Examiner's references comes only from the Appellant's disclosure in possession of the Examiner.

In the Final Office Action of January 11, 2005 the Examiner fails to meet the Patent and Trademark Office's legal responsibility to establish a *prima facie* case of obviousness supported by factual evidence. The Examiner has never provided objective evidence demonstrating a motivation to combine the Examiner's cited references. Whether a claimed invention is unpatentable for obviousness under 35 U.S.C. §103 is a question of law based on underlying findings of fact:

"The presence or absence of a motivation to combine references in an obviousness determination is a pure question of fact."[6]

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[6] *In re Gartside*, 203 F.3d 1305, 53 USPQ2d 1769 (Fed. Cir. 2000).

Lacking objective, factual evidence of a motivation to combine references, the Examiner distends the Quane reference to unsupportable dimensions. Accordingly, in the Final Office Action of January 11, 2005 the Examiner resorts to the construction of a conclusion-oriented argument that typically accompanies a hindsight analysis. Each of the Examiner's prior art references is at best a piece or component of the present invention. The Examiner makes no factual finding of a motivation to combine the teachings of Miller, Quane, Acta Anesthesiologica Scandinavica, La Du, Pharmacogenetics, Evans, Poort, Hoon, and Hacia. Contrary to legal requirement, the Examiner's conclusory and unsupported assertions are not evidence. The Examiner does not, and cannot, point to which particular teachings in the cited references motivate the ordinary artisan to combine the claimed elements and thereby arrive at the genomic profiles of the present invention for use in a perioperative subject.

As a consequence, the Examiner's assertions do not fulfill the obligation of the Patent and Trademark Office in establishing a *prima facie* case of obviousness. For example, nowhere in the prior art of record has the Examiner identified a teaching, suggestion or motivation to detect two or more nucleic acid genetic markers in two or more genes associated with two or more conditions in a sample from a perioperative subject to generate a genomic profile for use in selecting a perioperative course of action. If the Examiner is aware of such a suggestion or motivation, the Examiner is required to put it forward. Because the Examiner has never done so, the rejection must be withdrawn.

3. The Evidence Directly Refutes the Examiner's Rejection

In the Final Office Action of January 11, 2005 the Examiner speculates on what an artisan of ordinary skill would have been motivated to do. For example:

> "The ordinary artisan would have been motivated to have assayed for genetic markers prior to surgery to enable the detection of markers which are negatively associated with surgical conditions so that the conditions may be avoided." (Final Office Action of January 11, 2005, page 13)

As a factual matter, the Examiner is in error. To the contrary, at the time the invention was made ordinary artisans were not motivated to test patients for two or more nucleic acid markers in two or more genes known to be associated with two or more conditions to generate a genomic profile for use in selecting a perioperative course of action. The Examiner's argument for rejection on the basis of obviousness impermissibly couples the Examiner's incorrect, unsupported and conclusory guesses-in-hindsight about what an ordinary artisan "would have been motivated to do", with the Examiner's concessions regarding the invention's clear-cut and undisputed advantages. The Appellant contends that the Examiner's guesses do not satisfy requirements for establishing the *prima facie* case of obviousness. The Examiner's acknowledgment of the benefits of the present invention made in possession of the Specification and Claims, does not substitute for substantial evidence of what an artisan of ordinary skill would or would not have been motivated to do at the time the invention was made.

The Appellant does not need to provide any evidence to rebut the Examiner's failure to establish a *prima facie* case for obviousness, and for the Examiner's mistaken rejection to be overturned. Yet the Appellant has provided evidence. In order to further prosecution of the present case, and while under no legal obligation to do so, the Appellant has provided ample, easily understood and objective evidence in the form of published references, peer reviews, two Declarations, and a Practice Advisory. Contrary to the Examiner's speculations, this factual evidence consistently documents that at the time the invention was made, ordinary artisans did not agree with the Examiner's suppositions regarding the obviousness of perioperative genomic profiles. In the Final Office Action of January 11, 2005 the Examiner has mischaracterized and dismissed, but not contradicted, this evidence establishing that the Examiner's guesswork is in error. Rather than heeding the consistent message of the Appellant's direct evidence, and having failed to first established a *prima facie* case of obviousness, the Examiner seeks to apply an evidentiary standard of non-obviousness that represents a logical contradiction, *i.e.*, the need for a reference stating "don't do X" before the conception or invention of "X". Despite the Examiner's mischaracterizations and misconstructions of the objective evidence provided by the Appellant, these facts remain uncontested.

a.) **The Anesthesia Patient Safety Foundation (APSF) Review of the Grant "Perioperative Genomic Profiles" Stands for Non-Obviousness of the Present Invention**

As objective, factual evidence of the non-obviousness of the present invention the Appellant has provided the Examiner with a review of a grant application entitled "Perioperative Genomic Profiles". The review states:

> "The APSF committee members reviewing your proposal to study genetic profiles were impressed by the elegance to the proposal. It would take the issue of patient safety in a new direction." (Declaration of Kirk Hogan, M.D., February 8, 2002.) (Emphasis added.)

Hence, skilled artisans expressly articulate the non-obviousness of the present invention. Throughout subsequent prosecution and in the Final Office Action of January 11, 2005 the Examiner has avoided responding directly to this quotation. As well, the APSF review states:

> "As anesthesia practice has moved toward determining the ratio of quality to cost, this study seems to be going in the opposite direction. It suggests we test everyone in the hopes of finding something on almost everyone. The direction of anesthetic evaluation is presently to not routinely do any preoperative studies." (Declaration of Kirk Hogan, M.D., February 8, 2002).

The Examiner argues:

> "The committee does not appear to be establishing that given the art at the time of filing, that the invention was non-obvious" (Final Office Action of January 11, 2005, page 19.)

The Appellant contends that, contrary to the Examiner's conclusory argument,

the skilled artisans of the APSF review committee make precisely this point. Indeed, the Examiner has not and cannot dispute the finding of a committee of expert opinion that the perioperative genomic profiles of the present invention "would take the issue of patient safety in a new direction."

b.) Gregory and Kirby Stand for the Non-Obviousness of the Present Invention

In the Final Office Action of January 11, 2005 the Examiner argues:

> "The response provides references directed to the proposition that routine perioperative testing is unnecessary." (Final Office Action of January 11, 2005, page 20.)

Beyond directing the Examiner to the proposition that routine perioperative testing is regarded as unnecessary, the three references provided by the Appellant direct the Examiner to the proposition that testing patients for two or more nucleic acid markers in two or more genes known to be associated with two or more conditions to generate a genomic profile for use in selecting a perioperative course of action was non-obvious to artisans of ordinary skill at the time the invention was made. If, as the Examiner asserts, the prior art had contemplated the perioperative genomic profiles of the present invention they would have been taught, suggested or mentioned in Gregory, Kirby and Hopkins, particularly so if the Examiner's speculation is correct that there would have been a compelling reason to do so to avoid death and/or pain and suffering. Rather, Gregory, Kirby and Hopkins teach away from the perioperative genomic profiles of the present invention.

For example, Gregory in Pediatric Anesthesia, 2002 states, "The present consensus, therefore, is that routine screening tests are of little value." And that "There is a growing movement to omit all routine testing." Similarly, in Clinical Anesthesia Practice, 2002, Kirby states, "There are abundant data supporting the concept that routine laboratory screening tests are not cost-effective in the asymptomatic patient." To these factual and objective statements refuting the Examiner's assertions of the obviousness of

the present invention, in the Final Office Action of January 11, 2005 the Examiner replies:

> "While routine screening has not yet reached the point of being cost effective and highly efficient, the cited art still provides suggestion that with regard to the RYR1, BchE, prothrombin, etc. genes, testing prior to surgery would be certainly advantageous since mortality and complications may be avoided. While it is clear that many in the medical field do not believe that routine genetic testing provides sufficient valuable information to warrant its cost, this does not imply that the art has not conceived of or thought about perioperative genetic testing." (Final Office Action, January 11, 2005, page 21.)

In constructing this argument the Examiner has erred on a number of counts. First, the Examiner has failed to point to cited prior art that makes the Examiner's "certainly advantageous" suggestion. Second, it is not the Appellant's burden to prove a negative *i.e.,* to prove that the art has not conceived of the perioperative genomic profiles of the present invention. Rather, it is the Examiner's unmet burden to support arguments with more than guesses and speculation. For example, the Examiner has never put forward evidence that the prior art has in fact conceived of the perioperative genomic profiles of the present invention. Third, the Appellant has presented specific and abundant evidence of record teaching away from tests in the perioperative interval. The Examiner has never refuted this evidence as a demonstration of the non-obviousness of the present invention. Fourth, the Examiner's novel "certainly advantageous" standard of obviousness is not the law. In *In re Saung Su Lee* the Court of Appeals for the Federal Circuit expressly prohibits this kind of substitution of the benefits of an invention for objective evidence of an invention's obviousness by the Patent and Trademark Office.[7] Finally, the Examiner ignores objective evidence that skilled artisans at the time the invention was made did not recognize the benefits of the perioperative genomic profiles of the present invention let alone perioperative screening tests of any kind, and were not motivated to practice genomic profiling on the perioperative subject.

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[7] *In Re Sang Su Lee,* 277 F.3d 1338, 1341, USPQ2d 1430, 1433. (Fed. Cir. 2002).

c.) Hopkins Stands for the Non-Obviousness of the Present Invention

As further evidence that the Examiner's premises concerning the motivations of the ordinary artisan are in clear error, the Appellant has provided Hopkins, 2000, which states:

> "The complexity of the molecular genetics of MH (*i.e.*, malignant hyperthermia) described above precludes DNA-based diagnosis at present." (Amendment and Response to Final Office Action of October 24, 2001, page 10)

In the Final Office Action of January 11, 2005 the Examiner's argument in response to the Hopkins citation is tangential, and at odds with the remainder of the Examiner's rejection. For example, the Examiner asserts:

> "The claims are drawn to detecting two or more genetic markers to generate a genomic profile useful in selecting (a) perioperative course of action. The claims are not drawn to diagnosing MH." (Final Office Action of January 11, 2005, page 21).

Again, the Examiner makes a number of errors. First, claims of the present invention <u>are</u> drawn to diagnosing MH expressly (*i.e.*, Claim 94), and to the detection of mutations in genes causing MH (*i.e.*, 74-86, 91). Second, Hopkins expressly teaches away from the Examiner's incorrect interpretation of the Quane reference, which is cited and considered in Hopkins (Quane is reference #107 in Hopkins). Third, the Examiner has never refuted the direct evidence of Hopkins contrary to the Examiner's speculations regarding the motivations of an artisan of ordinary skill at the time the invention was made.

d.) The Second Declaration of Kirk Hogan, M.D., and the "Practice Advisory for Preanesthesia Evaluation: A Report by the American Society of

Anesthesiologists Task Force on Preanesthesia Evaluation", Stand for the Non-Obviousness of the Present Claims

In the Final Office Action of January 11, 2005, the Examiner argues:

> "The ordinary artisan would have clearly recognized the benefit of testing an individual prior to surgery and subjection to the anesthesia for known genetic markers associated with a condition which was triggered by anesthetics." (Office Action January 11, 2005, page 8-9). (Emphasis added.)

As still further evidence that the Examiner's conjectures concerning the motivations of the ordinary artisan are in clear error, in the Second Declaration of Kirk Hogan, M.D, the Appellant has introduced the 2002 publication "Practice Advisory for Preanesthesia Evaluation: A Report by the American Society of Anesthesiologists Task Force on Preanesthesia Evaluation". As detailed in the Declaration, the 12-member Task Force used a 6-step process to conclude:

> "Routine preoperative tests (*i.e.* tests intended to discover a disease or disorder in an asymptomatic patient) do not make an important contribution to the process of perioperative assessment and management of the patient by the anesthesiologist." (Second Declaration of Kirk Hogan, M.D., page 2).

As evidenced in both the manuscript and Dr. Hogan's Second Declaration, the Task Force Practice Advisory for Preanesthesia Evaluation does not teach that perioperative genetic testing should be carried out, does not provide guidelines for selecting markers useful for perioperative genetic testing, and does not advocate, consider or even mention genetic testing, use of genetic markers, or generation of genomic profiles. Thus, the Task Force Practice Advisory for Preanesthesia Evaluation explicitly demonstrates that both experts and artisans of ordinary skill in 2002 did not believe, and would not have "clearly recognized", that perioperative genetic testing should be carried out.

In the Final Office Action of January 11, 2005, the Examiner responds:

"This silence with respect to genetic testing does not mean that the testing would be unobvious. While the article may not specifically consider genotypes for preanesthesia evaluation [it] does not provide evidence that the combination of the cited references do not provide the legal standard for obviousness." (Final Office Action of January 11, 2005, pages 22).

The Appellant contends that it is not the Appellant's duty to prove a negative, *i.e.*, to prove non-obviousness. Rather, it is the Examiner's, and the Patent and Trademark Office's, duty to provide objective evidence of obviousness, that is, that the Examiner's combination of references do, in fact, meet the proper legal standard for obviousness. This duty has never been met in the course of prosecution of the present invention. Thus, it is not the Appellant's obligation to provide a reference in support of "the assertion that preoperative care precludes the testing of genetic markers" (Final Office Action of January 11, 2005, page 23.) To the contrary, the 2002 Practice Advisory, and all other objective evidence of record, stands in sharp contrast to the Examiner's lack of evidence, and erroneous guesses regarding what an ordinary artisan might have clearly recognized, or might have been motivated to do, at the time the invention was made.

Although it is not the Appellant's burden to demonstrate that the art had not yet thought of something that had not yet been created (*i.e.*, the perioperative genomic profiles of the present invention), the Appellant has furnished the Examiner with the best available evidence showing that, to the extent artisans have addressed the issue, there has been no motivation to move in the direction of the presently claimed invention. To assist the Examiner, the Appellant has put forward factual, plentiful and understandable evidence showing the Examiner's inability to fabricate a *prima facie* case of obviousness. In the Final Office Action of January 11, 2005 the Examiner has dismissed, but not contradicted, this evidence. As detailed above, to sustain the rejection the Examiner must put forth actual objective evidence. Instead, the Examiner has improperly concluded that because the invention is very useful, it must therefore be obvious. For these reasons the Appellant respectfully requests that the rejections be withdrawn.

B. Claims 84, 85, 92, 93, 99 and 100 are Allowable

In the Office Action of January 11, 2005 the Examiner argues:

> "The ordinary artisan would be motivated to design and tailor the mutations and probes on the array to meet their particular needs in detecting various mutations which are associated with particular surgical conditions or disorders. Hacia teaches screening for previously characterized sequence variants, all possible sequence variants (page 42, col.2)." (Final Office Action of January 11, 2005, page 28-29.)

And:

> "Here, the ordinary artisan would have expected that screening for variants which are known to be associated with surgical disorders, anesthesia reactions etc would have been obvious for the expected benefits of high accuracy and high throughput." (Final Office Action of January 11, 2005, page 29.) (Emphasis added.)

The Appellant contends that the Examiner's assertions are conclusory, and reflect confusion with regard to both facts and law. For example, the Examiner's speculations regarding what "the ordinary artisan would have expected . . . would have been obvious" is not a standard of law under 35 U.S.C §103. Similarly, the Examiner's dwelling on the "expected benefits" of the present invention is not a permissible substitute for objective evidence of a motivation to combine the Examiner's references. As well, in the Final Office Action of January 11, 2005, the Examiner ignores the Appellant's request to specify what text of Hacia or Hoon the Examiner considers to be the closest prior art for 5 or more, or 10 or more, nucleic acid markers in 2 or more genes drawn from the group consisting of *BChE, CYP2D6, MTHFR, MS, CBS, F2, F5, RYR1, CACNA1S, and CPT 2*, associated with 2 or more conditions to generate "a genomic profile for use in selecting a perioperative course of action". Nor does the Examiner specify what text in Hacia, Hoon, or in any other of the Examiner's references, provides specific guidance, general

guidance or any guidance whatsoever to the skilled artisan in selecting markers for inclusion in a genomic profile for use in selecting a perioperative treatment course of action, other than the guidance provided by the present invention's Specification and Claims. The Appellant contends that, read with the limitations of the independent Claims upon which they stand, Claims 84, 85, 92, 93, 99 and 100 are allowable.

C. Claim 101 is Allowable And Has Not Been Examined

Claim 101 reads:

> 101. A method of screening a patient perioperatively to determine a risk for complications during a surgical procedure from known genetic variations comprising:
>
> a) obtaining a sample from a perioperative subject, said perioperative subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure; and
>
> b) subjecting said sample to an assay for detecting two or more nucleic acid genetic markers in two or more genes clinically associated with butyrylcholinesterase deficiency and impaired debrisoquine metabolism to generate a genomic profile, wherein said genomic profile provides information for use by a physician in determining a risk for complications during a surgical procedure. (Emphasis added.)

In the Appellant's Amendment and Response to Office Action Mailed March 23, 2004, the Appellant makes plain to the Examiner that Claim 101 has not been examined and is allowable. (Amendment and Response to Office Action Mailed March 23, 2004, page 23). Specifically, Claim 101 does not claim the single gene (*i.e.*, the ryanodine receptor) or the single condition (*i.e.*, malignant hyperthermia) of Quane. Although the Examiner has failed to respond whatsoever to this accounting, the Examiner's rejection of Claim 101 is maintained under 35 U.S.C. §103 in the Final Office Action of January 11, 2005. Because the Examiner has never cited any reference that renders the combination of elements in Claim 101 obvious, the Appellant respectfully requests that the rejection be withdrawn.

F. CONCLUSION

In the course of prosecution of the present claims the Examiner has issued eight Office Actions (i.e., September 22, 2000, June 5, 2001, October 24, 2001, April 10, 2002, October 18, 2002, July 1, 2003, March 23, 2004, and January 11, 2005), successively raising and withdrawing a broad diversity of rejections. The Appellant notes that the MPEP expressly prohibits such piecemeal examination:

> Piecemeal examination should be avoided as much as possible. The Examiner ordinarily should reject each claim on all valid grounds available, avoiding, however, undue multiplication of references. (MPEP Section 707.07(g).) (Emphasis added.)

To the contrary, as a matter of record the Examiner has indulged in piecemeal examination as a *modus* of prosecution, arriving in the present circumstance at a multiplication of nine references that, nevertheless, still fail to meet the Patent and Trademark Office's burden.

For the foregoing reasons, it is submitted that the Examiner's rejection of Claims 74-94 and 96-105 was erroneous, and reversal of the rejection is respectfully requested. The Appellant requests that the Board render a decision as to the allowability of the Claims.

Dated: 9/19/05

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VIII. CLAIMS APPENDIX

1.-41. (cancelled)

42.-73. (cancelled)

74. (previously presented) A method of screening a patient perioperatively to determine a risk for complications during a surgical procedure associated with known genetic variations comprising:

a) obtaining a sample from a perioperative subject, said perioperative subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure; and

b) subjecting said sample to an assay for detecting two or more nucleic acid genetic markers in two or more genes associated with two or more conditions to generate a genomic profile for use in selecting a perioperative course of action, wherein said subjecting step occurs after said patient is scheduled for surgery but before completion of said surgical procedure, thereby determining a risk for complications during said surgical procedure.

75. (previously presented) The method of Claim 74, wherein said course of action comprises administration of anesthesia during a surgical procedure.

76. (previously presented) The method of Claim 75, wherein said surgical procedure is non-invasive surgery.

77. (previously presented) The method of Claim 75, wherein said surgical procedure is invasive surgery.

78. (previously presented) The method of Claim 74, wherein said course of action comprises administration of anesthesia during a medical procedure.

79. (previously presented) The method of Claim 74, wherein said genomic profile comprises information pertaining to a pharmacodynamic risk.

80. (previously presented) The method of Claim 74, wherein said genomic profile comprises information pertaining to a pharmacokinetic risk.

81. (previously presented) The method of Claim 74, wherein said genomic profile comprises a presymptomatic diagnosis.

82. (previously presented) The method of Claim 74, wherein said genomic profile comprises information pertaining to differential diagnosis of co-existing diseases.

83. (previously presented) The method of Claim 74, wherein said two or more nucleic acid genetic markers comprise mutations in two or more genes, said genes selected from the group consisting of *BChE*, *CYP2D6*, *MTHFR*, *MTR*, *CBS*, *F2*, *F5*, *RYR1*, *CACNA1S*, and *CPT2*.

84. (previously presented) The method of Claim 83, wherein said two or more nucleic acid genetic markers comprise 5 or more mutations in two or more genes.

85. (previously presented) The method of Claim 83, where in said two or more nucleic acid genetic markers comprise 10 or more mutations in two or more genes.

86. (previously presented) The method of Claim 74, further comprising the step of:

c) using said genomic profile for selection of conditions for a surgical procedure carried out on said patient.

87. (previously presented) A method for selecting conditions for a surgical procedure by screening a patient perioperatively to determine a risk for complications during a surgical procedure associated with known genetic variations comprising:

a) providing a sample from a perioperative subject, said perioperative subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure; and

b) subjecting said sample to an assay for detecting two or more nucleic acid genetic markers in two or more genes known to be associated with two or more perioperative phenotypes to generate a genomic profile for use in selecting a surgical procedure treatment course of action; and

c) subjecting said subject to a surgical procedure.

88. (previously presented) The method of Claim 87, wherein said genetic markers are associated with a pharmacological response.

89. (previously presented) The method of Claim 88, wherein said pharmacological response is to an anesthetic.

90. (previously presented) The method of Claim 88, wherein said pharmacological response is to drugs used in anesthetic practice.

91. (previously presented) The method of Claim 87, wherein said two or more nucleic acid genetic markers comprises a mutation in two or more genes associated with two or more conditions, said genes selected from the group consisting of *BChE, CYP2D6, MTHFR, MS, CBS, F2, F5, RYR1, CACNA1S, and CPT 2.*

92. (previously presented) The method of claim 91, wherein said two or more nucleic acid genetic markers comprises 5 or more mutations in two or more genes.

93. (previously presented) The method of claim 91, wherein said two or more nucleic acid genetic markers comprises 10 or more mutations in two or more genes.

94. (previously presented) A method of screening a patient perioperatively to determine a risk for complications during a surgical procedure from known genetic variations comprising:

a) obtaining a sample from a perioperative subject, said perioperative subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure; and

b) subjecting said sample to an assay for detecting two or more nucleic acid genetic markers in two or more genes clinically associated with two or more conditions selected from the group consisting of butyrylcholinesterase deficiency, impaired debrisoquine metabolism, thrombosis, and malignant hyperthermia to generate a genomic profile, wherein said genomic profile provides information for use by a physician in determining a risk for complications during a surgical procedure.

95. (previously presented) The method of Claim 94, wherein said course of action comprises administration of anesthesia during a surgical procedure.

96. (previously presented) The method of Claim 96, wherein said surgical procedure is non-invasive surgery.

97. (previously presented) The method of Claim 96, wherein said surgical procedure is invasive surgery.

98. (previously presented) The method of Claim 94, further comprising the step of:

c) using said genomic profile for selection of conditions for a surgical procedure carried out on said patient.

99. (previously presented) The method of Claim 94, wherein the said two or more nucleic acid genetic markers comprises 5 or more mutations in two or more genes.

100. (previously presented) The method of Claim 94, wherein the said two or more nucleic acid genetic markers comprises 10 or more mutations in two or more genes.

101. (previously presented) A method of screening a patient perioperatively to determine a risk for complications during a surgical procedure from known genetic variations comprising:

a) obtaining a sample from a perioperative subject, said perioperative subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure; and

b) subjecting said sample to an assay for detecting two or more nucleic acid genetic markers in two or more genes clinically associated with butyrylcholinesterase deficiency and impaired debrisoquine metabolism to generate a genomic profile, wherein said genomic profile provides information for use by a physician in determining a risk for complications during a surgical procedure.

102. (previously presented) A method for selecting an appropriate anesthesia treatment during surgery, comprising:

a) providing a sample from a perioperative subject, said perioperative subject being a patient scheduled for a surgical procedure that has not yet completed said surgical procedure; and

b) subjecting said sample to an assay that detects a first marker in a first gene and a second marker in a second gene to generate assay results, wherein said markers are known to be associated with adverse responses to anesthesia treatment;

c) subjecting said subject to a surgical procedure, wherein said assay

results are consulted in selecting an appropriate anesthesia treatment for said subject.

103. (previously presented) The method of Claim 102, wherein said selecting comprises selection of dosages of anesthesia.

104. (previously presented) The method of Claim 102, wherein said selecting comprises selection of anesthesia compounds.

105. (previously presented) The method of Claim 102, wherein said selecting comprises selection of monitoring procedures.

IX. EVIDENCE APPENDIX

Two Declarations filed February 8, 2002 and July 8, 2002 are of record.

X. RELATED PROCEEDINGS APPENDIX

No decisions have been rendered by a court or the Board in any proceeding identified pursuant to CFR §41.37(c)(1)(ii).